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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/976,886 | Applicant(s) Rimm et al. |
|---|---|---|
| | Examiner Yvonne Eyler | Group Art Unit 1642 |

☒ Responsive to communication(s) filed on *Dec 26, 1999* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-14* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

**Response to Amendment**

Claims 1-14 are pending and under consideration in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections Maintained:***

1. The rejection of Claims 1-14 under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained but will be separated into two rejections, as per applicants objection to their combination. Applicant has requested any judicial precedence for the original combination of the rejections. As per applicants request, attached to this Office Action are copies of *Ex parte Ishizaka* 24 USPQ2d 1621, 1992, *Ex parte Tanksley* 37 USPQ2d 1382, 1994, and *In re Angstadt and Griffin* 190 USPQ 214, 1976.

2. The rejection of Claims 1-14 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record as detailed on pages 4-8 of the Office Action of 6/23/99 and as detailed below.

Applicant observes that the claims cannot be read in a vacuum and need only set forth and circumscribe the particular area with a reasonable degree of precision and particularity. Applicant

also argues that the claims need only be measured against the knowledge of the art and not against the knowledge of a patent examiner.

These arguments have been considered but are not found to be persuasive.

-The basis of rejection over "abnormal" cells, found in claims 1, 2, 8, 9, (dependent claims 10, 11, 12), and 13 is maintained for reasons of record. While cancer cells are pathologically abnormal nucleated cells, pathologically abnormal nucleated cells are not limited to cancer cells or precursor hematopoietic cells. The terms normal and abnormal are subjective terms of degree, which may be subject to individual interpretation. There is no definition within the specification regarding the limits at which normality ends and abnormality begins such that the metes and bounds of what is within the scope of the claimed invention may be clearly determined. The specification exemplifies two species of abnormal nucleated cell, but does not define the claim term abnormal to be limited to these two species. While the claims are read in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The specification, while presenting only methods of detecting cancer cells and precursor hematopoietic cells, does not provide a limiting definition of the instant phrase. If the intent is to limit the invention to the exemplified and clearly defined species of methods of detection of cancer cells, then the claims should be amended to clearly state for example, -A method of detecting the presence or absence of circulating cancer cells in an anticoagulated whole blood sample...-

- the basis of rejection over "well-defined zone" or "well-defined annular zone," found in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, (dependent claim 10), 11, (dependent claim 12), 13, and 14 is maintained for reasons of record. Applicant argues that the paragraph bridging pages 4 and 5 and the prior art cited therein eminently describes commercially available paraphernalia having such a well-defined zone. Applicant further argues that the well-defined zone is clearly illustrated in Figures 1 and 3-

14. This has been considered but not found to be persuasive. The specification at pages 4-5 does not define the phrase "well-defined zone." The specification at pages 4-5 describes a cylindrical float that creates a free volume between the walls of the tube and the float itself, into which volume the pathologically abnormal nucleated cells will layer. Claim language along these lines would be clear, concise, and definite. Figure 1 and it's description on page 12, does not depict or define a "well-defined zone." Figure one refers to a lower end, however. Figures 3-14 are photoimages of scans of blood samples and do not describe a "well-defined zone." Figure 2, although not cited, does refer to a zone, but it appears that the zone of figure 2 is that through which the optical beams pass. U.S. Patent Nos. 4,027,660 and 4,082,085, columns 3-4, teach a tube bore, with a cylindrical insert whose diameter is smaller than the tube bore forming a free space of restricted volume which is occupied by white cells and platelets. Column 6, lines 13-28 refers to a zone, but those zones are multiple and not "well-defined," and are in reference to upper and lower layers within the tube. U.S. Patent No. 4,156,570 does not appear to refer to a zone. Therefore, given the lack of description of the metes and bounds of what is encompassed by the phrase "well-defined zone" within the instant specification, plus the lack of clear description of such a term in the prior art, the phrase is maintained to be indefinite.

- The basis of rejection with regard to "epitopic-specific labeling agents", "epitopic labeling materials", "epitopic-specific which highlight", or "epitopic-specific agents which signal" is maintained for reasons of record. Applicant argues that the specification on pages 6-8 clearly disclose the target, labels, binding agents and binding sites. This argument has been considered but is not found to be commensurate with the claimed terminology. The specification does not define what chemicals, molecules, structures etc. are encompassed by the terms agents or materials and how they are identified. The disclosure of antigens, antibodies, or receptors which specifically bind to markers present on the target cells does not define the metes and bounds of the term agent. Amendment of the claims to recite -combining the blood sample with a one or

more antigens or antibodies which specifically bind to the target cells- would be one way to overcome the rejection.

- The basis of rejection over "stains or colorants that clarify cell morphology" or "cell morphology clarifying stains" is withdrawn in light of applicants arguments.

- the basis of rejection regarding "clarified morphology" is withdrawn in light of applicants arguments, however, the basis of rejection regarding "abnormal morphology" is maintained for reasons of record and as detailed above with regard to abnormal nucleated cells. Applicant argues that a cytopathologist would know how to distinguish normal cell morphology from abnormal cell morphology. This is not found persuasive because the terms normal and abnormal are subjective terms of degree, which may be subject to individual interpretation. There is no definition within the specification regarding the limits at which normality ends and abnormality begins such that the metes and bounds of what is within the scope of the claimed invention may be clearly determined. As discussed supra, the term abnormal cell is a generic term that encompasses more than the two exemplified species. The specification does not provide a clear and concise definition such that any other species of nucleated cell may be unequivocally identified and the exemplification of two species is not a limitation that is read into the claim. This basis of rejection may be overcome by limitation of the claims to phrases such as -combining the blood sample with a morphometric stain which clarifies cell morphology in all nucleated cells.-

- The bases of rejection regarding "differentiate" are withdrawn. It is found persuasive that, read in light of the specification, one would know that the terms mean that abnormal nucleated cells

are distinguished from normal cells and that the term does not refer to developmental differentiation from a precursor stage cell to a mature cell.

-With regard to a Lack of clear correlation step, this rejection is maintained with regard to claims 3. Applicant argues that there is no factual basis for this rejection. This argument is found to be partially persuasive, for example, claims 1, 2, 5 , 7, 8, and 9-14 are clearly drawn to a method of detecting/enumerating a specific cell and conclude with that detection. While a correlation step, per se, is not present, a correlation is step within these claims is not necessary to clearly claim the intent of the method. However, with regard to claim 3, the preamble states the intention to be enumeration of circulating epithelial cells but the end result is the enumeration of labeled epithelial cells having pathologically abnormal morphology. The stated goal and the end result are not equivalent in scope, as only a subset of circulating epithelial cells were enumerated, namely those having pathologically abnormal morphology. This may be clarified by amending the preamble to match the end result. Claim 4 also is not consistent between the stated preamble goal and the end result. The preamble states a method for differentiating cancer cells from hematologic progenitor cells and from other nucleated cells. The end statement recites determining any differentiated nucleated cells present. This recitation does not clearly state the intended goal, i.e. which differentiated nucleated cells are determined to be present? Cancer cells, hematologic progenitor cells and other nucleated cells are all nucleated cells that are supposed to be differentiated from each other, according to the preamble. The end step does not clearly reflect this three-way differentiation. Claim 6 also shares this discrepancy. The preamble of claim 6 recites that a sample will be analyzed for the presence or absence of cancer cells and/or hematologic progenitor cells, but the end result detects the presence of any differentiated nucleated cells, which again does not clearly indicate the successful three-way differentiation of cancer cells from hematologic progenitor cells from other nucleated cells.

-the basis of rejection over Claims 2 and 14 not specifying when the blood sample is centrifuged is withdrawn, while the claims do not clearly state when the centrifuging occurs, one of skill in the art would be able to determine how to practice the method.

- the rejection over a"percentage of all labeled cells" found in Claim 2 is maintained. The phrase "a percentage of all labeled cells" has multiple interpretations and it is not clear which one is intended. For example, the phrase could indicate that a predetermined portion of all labeled cells will be examined, i.e. perhaps 20% of the total labeled cells will be examined. This could also indicated that the number of cells in the "zone" are counted and compared to the total number of cells present in the entire tube in order to determine the actual percentage of cells present in the "zone." The referral to the algorithm on page 20 does not clarify the interpretation because the algorithm is drawn to determining the total number of cancer cells in a sample based on the partial portion of a sample that is examined. This algorithm does not define the phrase "a percentage."

- The basis of rejection over the order of steps of Claim 3 is withdrawn.

- the rejection of "constituent components of blood" in claims 4, 5, and 6 is maintained. Applicant has amended the claims by inserting "formed" to clarify which constituents, however, the actions encompassed by this term are not defined such that it may clearly be determined what is included as a "formed constituent." One way to overcome this rejection would be to amend the claims to recite separating the blood sample into its cellular constituent components.

- The basis of the rejection over "insert that is operable" in Claims 4, 5, and 6 is maintained. Applicant argues that the insert necessary to perform the recited functions is commercially available and therefore it's characteristics may be identified. This argument is not found to be persuasive or commensurate with the claimed invention. Claims 4, 5, and 6 are not limited to a specific, commercially available insert and tube paraphernalia. Further, as discussed supra the language of "well-defined zone," which is the recited function, is not clearly and concisely described in the specification or the prior art such that the insert that performs the function may be unequivocally identified. Further, where a trademark or trade name, such as the instant QBC$^{R}$ paraphernalia, is used as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. The language of the claims could be clarified by reciting, for example, that the insert is a cylindrical float that creates a free volume between the walls of the tube and the float itself, into which volume the pathologically abnormal nucleated cells will layer, which language is supported by the specification which was, contrary to applicants contention, considered in depth upon each review of the application.

- The rejection over inconsistency between claims 4, 5, 6, 9 and 13 is withdrawn. The claims appear to be drawn to different methods, the apparent inconsistency arising as a result of the unmatched preamble and end steps as a discussed supra.

- The rejection over "Axially elongated insert" in Claims 7 , 9, 13 is withdrawn. There are only a limited number of reasonable axes available. Any lack of clarity is the result of the term "well-defined zone" which has been discussed supra.

-The rejection over "microscopical instrument" in Claim 10 is maintained. Applicant argues that the term means something that resembles a microscope, or is like a microscope but is more than a conventional microscope. The instruments encompassed by this description cannot be determined. The definition of conventional microscope is not provided and it is not clear what instruments are considered to be conventional and what are not. Further the description of like a microscope but more is not clear because there is no definition of what is encompassed by "more." Applicant refers to Figure 2 in support of the description. Figure 2 depicts and clearly describes an "automated colorimetric microscopical instrument assembly" used to scan the centrifuged blood sample. Amendment of the claim to include such clearly defined and precise language, supported by the disclosure, would overcome the rejection.

-the rejection over "predetermined power" in Claim 11 is maintained. Applicant argues that a cytologist would know what power of magnification to use to examine cells. This argument is not commensurate with the claimed invention. The phrase "at a predetermined power" indicates a specific power of magnification is being specified, but this specific power, which was predetermined, is not set forth. While a cytologist would know how to select a power of magnification in order to examine cells, said cytologist could not select the specific predetermined power indicated without more information regarding what that power is. The indefiniteness may be eliminated by amendment along the lines of "The method of claim 10, wherein said free volume or zone into which the pathologically abnormal cells migrate, has a transverse thickness which is essentially equal to the focal operating range of said microscopical instrument assembly.

-the rejection over "signal result" in Claim 14 is maintained. Applicant argues that the signal result is clearly described in the specification and merely refers to the signal produced by a particular labeling agent and emanating from cells with said label. This argument is not commensurate with the claimed invention. The claims refers to a labeling agent operative to produce a characteristic signal result which can result in no signal at all. This does not clearly and concisely describe the labeling and detection of cells as a applicant indicates is intended. Amendment of the claims to language such as a: -said blood sample having been combined with one or more labeled antigens or antibodies which specifically bind to the target nucleated cells, producing a signal which may be detected in order to determine the presence of target cells.-

3. The rejection of Claims 1-14 under 35 U.S.C. 112, first paragraph, as a containing subject matter which was not described in the specification in such a way as a to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

Applicant argues that rejections under 112 first paragraph are directed to the requirements of the specification and that the clarity of the claims under 112 second paragraph does not raise issues of enablement. Applicant requests citation of case law which explicitly supports such a situation.

This argument has been considered but is not found to be persuasive. a rejection under 112 first paragraph was applied in *Ex parte Ishizaka* 24 USPQ2d 1621, 1992, based on the inability to neither determine the intended scope of the claims nor find adequate enabling support

for the breadth that would seem to be attributable to these claims (see page 1626 of the enclosed opinion). Similarly, a rejection under 112 first paragraph was applied based on ambiguity of the scope of the claimed invention in *Ex parte Tanksley* 37 USPQ2d 1382, 1994, see page 1387 of the opinion.

Similar to these situations, the intended scope of the claims cannot be determined and the resulting apparent breadth of claimed invention is not enabled by the specification. The specification discloses the discrimination of cancer cells or hematologic progenitor cells from other nucleated cells within a blood sample by specifically labeling the cancer cells or progenitor cells and detecting that label. The cells may be further stained with a morphometric stain in order to increase contrast and facilitate examination of cellular features. The specification does not provide guidance enabling one of skill to determine the presence of any nucleated cell associated with any pathology or the presence of any abnormality, which is undefined. The correlation between the presence of nucleated cancer cells in the peripheral circulation and the presence of cancer does not provide objective evidence of a predictable correlation between the presence of any other nucleated cell or abnormal cell with any unknown pathologies. The specification does not provide guidance in the detection of the breadth of cells and pathologies encompassed by the claim language.

Further, the specification discloses a single species of tube and float paraphernalia assembly which enables one of skill to detect cancer cells. That assembly comprises a tube into which is inserted a cylindrical, elongated float having a density equivalent to that of nucleated

lymphocytes, which is smaller in diameter than the tube and results in a free space between the tube wall and the float. Upon density gradient centrifugation, nucleated cells migrate to this free space and may be visualized and distinguished. The specification does not provide guidance regarding the design of insert and tube paraphernalia commensurate in scope to the apparent breadth of the claims. The definition of a "well-defined" zone is ambiguous, rendering it unclear where in the tube this zone is and how it is identified. The insert is claimed only as a cylindrical, or elongated, or operable to form the "well-defined" zone. The number of design choices commensurate with this language cannot be determined and there is insufficient guidance provided regarding how to design or make an assembly, other than the single species provided, which would predictably be used to detect any pathological nucleated cell.

The specification discloses labeling of target cancer cells, or hematological progenitor cells, by specifically binding antigens or antibodies conjugated to a detectable label to cell markers. The specification does not provide guidance of how to identify or make other agents or materials which are epitopic specific such that one of skill would be enabled to practice the full scope of the invention, as a claimed.

Several detailed limitations are also ambiguous such that the scope of the claimed invention may not be practiced absent undue experimentation. As a stated supra, claims 3, 4, and 6 recite inconsistent preamble and correlation steps. While one of skill in the art would be enabled to enumerate target cancer cells by detecting epithelial cells labeled with a cancer specific antigen or antibody, which does not bind to hematologic progenitor cells, one would not be enabled to

enumerate any and all circulating epithelial cells by differentiating and detecting only those having pathologically abnormal morphology as a recited in claim 3 or to enumerate cancer cells by detection of all nucleated cells as a recited claims 4 and 6. One of skill would also not be enabled to identify the claimed percentage of cells in claim 2, since the interpretation of how to calculate that percentage is unclear. One of skill in the art would not be able to determine how to centrifuge the blood sample commensurate in scope with the claimed invention of claims 4, 5, and 6. The specification discloses density gradient centrifugation sufficient to separate cellular components, however, there is insufficient guidance regarding how to predictably separate any other components of a blood sample as a encompassed by the claims. One of skill in the art would also not be enabled to analyze the centrifuged samples at an unknown, predetermined power absent guidance regarding what that specific predetermined power is, nor would one of skill be enabled to examine the cells using any microscope like instrument which is not a microscope commensurate in scope with the claims.

Thus, the apparent scope of the claimed invention, due to the ambiguity of the claim language, is not enabled by the instant specification, absent undue experimentation.

4. The rejection of Claims 1-14 under 35 U.S.C. 103(a) as a being unpatentable over Levine et al. (U.S. 5,834,217) and Rickman et al. (The Lancet. Vol. I, pages 68-71, 1989) in view of

Nagy et al. (The J. of Exfoliative Cytology.-IDS) and Goldblatt et al (The J. of Exfoliative Cytology.-IDS) is maintained.

Applicant argues that the characterization of the claimed method completely ignores the differentiation aspect of the invention. Applicant further argues that Levine et al does not detect individual cells, only cell bands. Applicant also argues that Rickman et al. Does not teach detection of individual cells, either, but rather only cell layers and parasites. Applicant argues that no suggestion to epitopically label different types of target cells in order to differentiate them is set forth. Applicant argues that no determination of a percentage of labeled cells in a blood sample is set forth. Applicant argues that no separation of cancer cells from HPC's is set forth, nor is suggestion made of where to look for the cells in centrifuged blood samples. Applicant concludes that the rejection does not address every limitation of the claimed invention and does not address each claim.

These arguments have been considered, but are not found to be persuasive. The claimed invention was not rejected over any single prior art reference, alone, but rather, over the combined teachings of the prior art as a a whole. Further, the prior art was found to suggest each and every aspect of the claimed invention.

Levine et al.teaches that it was known in the prior art that target analytes within a blood sample, including nucleated cells, may be separated into different areas of the QBC tube and identified based on specific, epitopic labeling of the target analyte with antigens or antibodies, which labeling emits a signal that is quantitated. Levine et al. also teach to stain the nucleated cells

with a DNA stain. Target nucleated cells are taught to be separated (differentiated) from other nucleated cells, i.e. lymphocytes and the proportion of target nucleated cells within the blood sample is calculated. Also taught is differentiation of lymphocyte subsets from each other and the differentiation and detection of hematopoietic progenitor blood cells by specific labeling of CD34. (See the abstract; column 2, lines 40-67; column 3, lines 8-14 and line 58 to column 4, line 3; column 6, lines 27-34 and line 66 to column 7, line29; column 9, lines 52-67; column 10, lines 40-55; and column 11, lines 14-18) Thus, differentiation of target cells by epitopic-specific labeling was known. Differentiation of target cells by separation into different zones within a QBC tube by density centrifugation was known. Quantitation of the proportion of target cells out of total nucleated cells or sample cells was known. Staining of target cells with morphometric stains was also known. Levine et al. do not detect individual cells.

Rickman et al. teach that processing diagnostic blood samples with the QBC tube is easier and much more rapid then processing blood smears, and just as a sensitive in the differentiation of target cells from other blood cells. Rickman et al. teach differentiation, or separation, of blood cells using the QBC tube and that nucleic acid containing cells (i.e. nucleated cells) around the float may be viewed by microscopy. Rickman et al. viewed individual cells (see column 1 on page 69, last line of the second full paragraph) within this layer and identified malaria parasites. (See the summary, introduction, and materials and methods). Thus, nucleated cell differentiation into different zones by QBC was known in the prior art as a was microscopic evaluation and differentiation of individual cells within the tube. Applicants argument that individual parasites

were identified, not individual cells, is not found to be persuasive, since malarial protozoa, such as a *P. Falciparum* are unicellular and since Rickman et al. specifically state that "individual cells within this layer are easily seen by microscopy." Further, Rickman et al. viewed the cell samples at magnification of X750 to X1000, which is comparable to the instantly contemplated magnifications and would be reasonably expected to facilitate detection of individual cells.

Thus, as a taught by Levine et al. and Rickman et al. differentiation of different nucleated cell types by centrifugation in QBC tubes was known. Detection of hematopoietic precursor cells by this method was known. Further, labeling target cells by antigen/antibody binding was known. Staining with morphometric stains, in addition, was known. Microscopic detection and examination of individual cells within the space around the float was known.

Neither Levine et al. or Rickman et al. teach cancer cells as a the target cell.

Nagy et al. teach that detection of cancer cells in the circulation was known to be diagnostic for cancer. Nagy et al. teach separation of nucleated cells by density centrifugation-cancer cells settle with the nucleated cells, followed by preparation of a smear, staining with a morphometric stain, and microscopic examination of individual cells (see page 61).

Goldblatt et al. also teach that detection of cancer cells, including by immunofluorescence in the circulation was known and diagnostic and review several different methods, including a flotation method, by which cancer cells are isolated from other cells and detected. (see the entire article especially pages 6 and 14). Applicant refers to the negative teachings in the summary of Goldblatt et al., however, Goldblatt et al. was cited for the plethora of methods known to detect

cancer cells in the circulation. That cancer cells in the circulation have diagnostic value has been well established since the publication date of Goldblatt et al, as a evidenced by Nagy et al.

Thus, the detection of nucleated cancer cells within blood samples was also known, and that said cells were separable by density centrifugation, i.e. one would know where to find them in a centrifuged sample.

The combined teachings of the art are that the separation of nucleated cells by QBC centrifugation combined with immunolabeling was known. Further the microscopic evaluation of individual cells within the QBC sample was known to be superior to blood smear analysis. Further, cancer cell diagnosis by blood smear analysis was known and cancer cells were known to centrifuge with nucleated cells in the blood.

It is maintained that it would have been *prima facie* obvious to one of ordinary skill in the art to modify the QBC technique to morphologically detect and quantitate individual nucleated, epithelial cancer cells with a reasonable expectation of success because individual nucleated cell detection and quantification was known as a taught by Levine et al. and Rickman et al. It was also known in the art that cancer cells (which are nucleated and epithelial) were present in the blood, separable with lymphocytes, and diagnostic of cancer. One would have been motivated to do so because Rickman et al. teach the advantages of rapid, mass screening using QBC.

NO CLAIM IS ALLOWED.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as a set forth in 37 CFR 1.136(a).

a shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**paula.hutzell@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler

Yvonne Eyler, Ph.D.
Primary Examiner
March 9, 2000